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CHEMISCHE WERKE ALBERT & OTHER PHARMACEUTICAL TARGETS WEISBADEN.

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COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE

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CHEMISCHE WERKE ALBERT AND OTHER PHARMACEUTICAL TARGETS IN THE WIESBADEN AREA

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CIOS Target No. 24/162
Medical

COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE
G-2 Division, SHAEF, (Rear) APO 413

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I. Chemische-Werke Albert, Wiesbaden-Biebrich

1. Introduction

This plant was visited on 29 June 1945. It makes mainly plastics, heavy chemicals, and fertilizers. As a result of work on phosphates, it went into the pharmaceutical field. The first product was Recresal, which is calcined sodium dihydro-orthophosphate.

The plant was severely bombed September 19, 1944 in daylight. In about one minute over 200 bombs were dropped, destroying about 50% of the plant. It still is not in operation due mainly to lack of raw materials and coal. Phosphate rock was obtained from North Africa, and was low in fluorine.

In the pharmaceutical field, all manufacturing is done at Säckingen on the Swiss border. All research is done at the Wiesbaden-Biebrich plant. The pharmaceutical research staff is not a large one, but the quality of the work is good. Dr. Emil Tidebenz is the main research chemist and Dr. Winkler is the managing director.

The products manufactured by the Albert Co. are as follows:

Recresal (mixture of sodium phosphates)
Lubrokal (K Br luminal)
Neo-Lubrokal (K Br luminal (tetrahydro-p-oxagino) methyl phenyl ketone)
Xylidrin-preparations (a mixture of synthetic B, B-diphenyl-b-hydroxzedrylamines)
Hämo-xylidrin (same as xylidrin)
Turgasept (one of the synthetic B, B-dipheryl-B-hydroxzethylamine)
Euklimon (Mixture of herb extracts with nitroglycerine)
Carbarom (medical charcoal with Aluminum hydrosilicates)
Albertstine (an antiphlogistic agent)
Cholagutt (mixture of herb extracts)
Vutox (aqeous solution of xylidrin)

This list constitutes the entire pharmaceutical business of the Albert Co. The products in the above list which are synthetic organic compounds are the result of Dr. Tidebenz's researches, and are apparently well thought out products based on sound research. The others are either old preparations of simple inorganic salts or are shot-gun preparations consisting mainly of herb extracts.

These preparations will be discussed separately because several of them, particularly the synthetic ones, show originality.

2. Recresal is a mixture of sodium phosphates for use in providing readily available phosphorus. It was placed on the market on the basis of work done by Professor Embden at the University of Frankfurt. It was stated by Dr. Eidebenz that this preparation was found to be utilized very well clinically and better than organic phosphate esters. This point is open to question, but, nevertheless, the product seems to be well thought of in Germany. D.R.P. 711 339 10/2/44 covers this material patentwise. It is of interest also as it represents the starting point of the pharmaceutical business of the Albert Co.

Further researches on phosphorus-compounds are in progress. These are of two types. One has to do with the combination of the phosphate radical with Vitamin B. Specifically, the preparation of the phosphate ester of B is under consideration. The second line of research is in the field of iodo-phosphate esters of organic alcohols. For example, Eidebenz has prepared 1-iodo-2, 3-dihydroxzpropane-phosphate 3 (Arch. Pharm, (1942, 227). This product is on clinical trial.

3. Lubrokal is a physical mixture of potassium bromide with sodium luminal. The statement was made that the presence of the bromide potentiates the action of the barbituric acid so that a lower dose is possible. This is not new as papers on this subject have appeared in the American literature. The preparation sold by the Albert Co. contains 0.04 g of sodium luminal and 0.6 g of K Br per tablet. While the men interrogated seemed to think this product was a real contribution, it would appear to us to be of only minor importance.

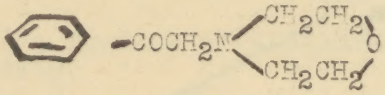
Many papers have appeared in the German literature reporting clinical studies of Lubrokal. Among these is the following:

(a) Med. Welt. (1927) by Dr. Berr in No. 4. This is a clinical report from the Frankfurt/M city hospital.

The Albert Co. also has recommended a systematic cure for insomnia, using this substance. A brochure describing this treatment is given as Appendix I.

4. Neo-Lubrokal. This preparation is a physical mixture of potassium bromide, sodium luminal and a new spasmolytic compound.

The Albert Co. has made a rather intensive search for a suitable compound of this type. The one finally decided upon was M.K. 138 and has the structure:



The pharmacology of this mixture is reported in Münch. Med. Wochenschrift. (1940) No. 8 by Dr. H. Kionka of Wiesbaden.

The tetrahydro oxazine compound has been patented in Germany as have other compounds in this general class. These patents are:

667358	11/9/38
671786	2/13/39
688675	2/28/40
710397	9/12/41
733300	3/24/43
740879	11/2/43

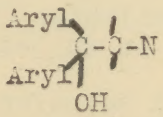
Clinical reports on Neo-Lubrokal are in -

Med. Welt 14,1300 (1940)
ibid. (1940) No. 51 (Dr. Hoffmann)
Kinderärztliche Praxis II No. 12 (Dr. Aug)

The preparation is recommended for use as a general hypnotic.in nervousness and allied ailments. It is marketed in the form of tablets containing 0.6 g K Br, 0.03 g luminal and 0.05 g M.K. 138. Again the Albert Co. thinks highly of this substance, but it does not appear to us to be too important. The spasmolytic substance M.K. 138 is alleged to have an acetyl choline-like action and for this reason M.K. 138 might be investigated as a substitute for acetyl choline.

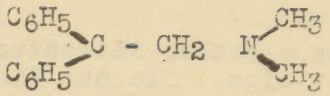
A patent on the compound M.K. 138 has been applied for in the United States of America, but is probably one which has been seized by the alien property custodian.

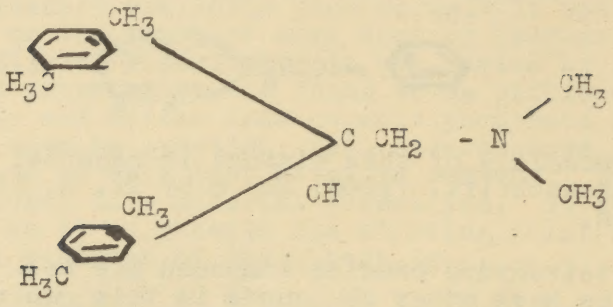
5. Xylidrin-preparations. These substances all have the general formula



Specifically two of these are used in combination in Xylidrin oleum.

These are -

(a) 

(b) 

These two substances are alleged by Eidebenz to have very interesting properties.

(a) has an ephedrin-like action (this is to be expected);
(b) has a bacteriostatic activity and also a local anesthetic activity

Both substances are stated to exhibit all three of these properties but the main effects are those listed above for each substance.

This product is recommended as a vasoconstrictor for colds and inflammation of the mucous membrane. It is sold as an oil for nose drops or as a salve.

The preparation of substances in this class is described in Arch.Pharm. (1942), No. 49 and in D.R.P.-

651543	10/16/73
675817	5/17/39
681849	11/3/39
682876	10/24/39
694005	7/23/40
713257	11/4/41
725844	10/1/42
735419	5/14/42

Translation of a pamphlet describing the properties of these substances is given in Appendix 2.

6. Hämo-xylidrin contains the same two substances as xylidrin, but is made up in suppositories for hemorrhoids.

7. Turgasept is an oil solution of the compound (b) in glycerin used in the xylidrin preparations. This preparation is used in the ear, for otitis media.

8. Dukliman. This is a preparation for neuralgia. It contains nitroglycerin, agaricin, extractum hyoscyami, ol. salvae, cineol and ol. rosemary. This is a first class shot-gun preparation.

9. Carbarom is a mixture of aluminum silicate and charcoal for hyperacidity.

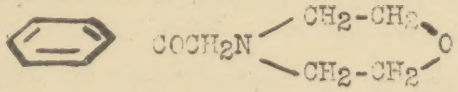
10. Albertistine is an antiphlogistic preparation containing glycerine, bentonite and ichthyol. Bentonite is the main ingredient.

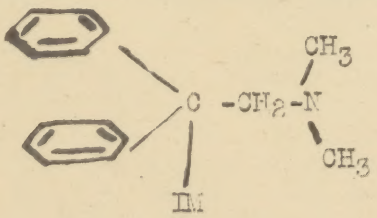
11. Cholagutt is another preparation made of vegetable extracts. It is used for "inflammation and excitation of the liver-bile-system".
It contains extracts of Chellidonium maisas, agaricium and other extracts.

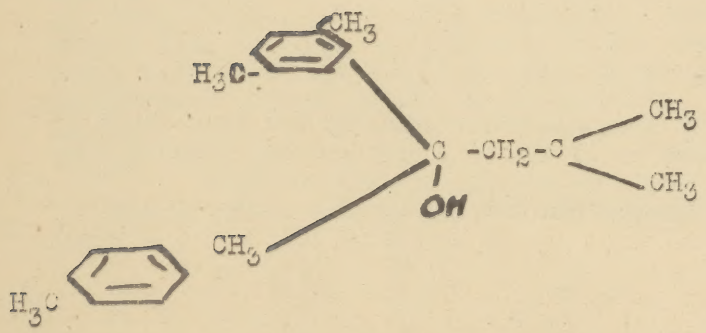
12. Vutox is an aqueous preparation containing hydrochlorides of the xylidrin series.

13. Summary.

As can be seen from the types of products made, most of them are of no importance. It is believed, however, that notice should be taken of -

(a) 

(b) 



(c) Antipyretics of the pyrazol class described in Arch. Pharm. (.943) No. 171. These are also described in D.R.P. 716481, 1/21/42.

II Pharma, G.m.b.H, Mainz. This plant was visited on June 29, 1945. It was located and found to have been demolished by bombing and fire. It was a small business, specializing in filling ampoules and other drugs. No evidence of manufacturing could be seen in the ruins.

III Kolle & Co. A.G., Biebrich, a.R. This plant was visited on June 29, 1945.

It is a subsidiary of I. G. Farben and makes cellophane and cellulose for photographical uses. It has no pharmaceutical interests.

IV Dr. Fhilo & Co., Mainz, 15 Weisenauer Str. (Owner: Dr. Julius Fhilo).

This plant was found to be burned out except for the packing and shipping room. No manufacturing was done here. Full line of ampoules and tablets. Most products were brought from I. G. Farben, some apparently from Merck.

This place seems to be known under at least two other names - "Eifelfango" and "Aethylia". None of the management could be found.

APPENDIX I

The Lubrokal Cure

Introduction to the Courses of Treatment

Insomnia and 'nerves' are often closely connected in their origins; nervous excitement causes sleeplessness and the want of proper rest in its turn enhances the nervous state. Treatment hitherto prescribed in such cases has been in the form of sleeping drafts and nerve tonics. The task, however, of a casually directed therapy must be to break the vicious circle at the real seat of the trouble and give it a contrary direction - namely along the road to health.

The Lubrokal cure fulfills this requirement. It achieves at the same time a soothing of the nerves and restores the sufferer to a state where he can enjoy proper rest by means of small dosages of Bromides and Barbituric Acid; frequently it leads to a complete cure.

In order to obviate errors on the part of the patient which might jeopardise the success of the cure, the following instructions should be adhered to:- But first, a word about the cause;

A fundamental error of treatment in the means adopted previously has been to look upon sleeplessness as the trouble itself and attempt to remedy it. It has not been realized clearly enough that insomnia is not in itself a primary malady but owes its existence to nervous excitement having its origin in the relevant centres in the brain and only engaging secondarily the nerve-centres connected with the state we know as sleep through sympathetic excitation. Hydrotherapeutic and psychotherapeutic measures have for their aim an attack on the sources of the trouble themselves, but the causal state of irritation, excitement of the nervous system, which is of such great significance, has been strangely neglected in courses of treatment for sleeplessness in the past. Sleeping drafts have been prescribed which,-to be sure-enable the patient to achieve sleep when he goes to bed but these never reach down to the real source of the trouble, the sleep disturbing nervous excitement which caused it originally, and consequently, no real cure is achieved. Treatment which will banish the primary malady has two tasks to fulfil;

the treatment of the primary cortical excitation of the nervous system as the overwhelming cause of the state, and-

the inducement of sound, dreamless sleep by the soothing of the sleep centres of the brain, taking this as the real source of the trouble.

The sedative-hypnoticum "Lubrokal" (bromide - barbituric acid) is able to carry through both tasks, as it is the most effective medium in the treatment of the nerves centres in the cerebral corticum and the best known medium for soothing the sleep centres in the brain and it unites the two mediums in an accurately balanced optimal combination. Since both components are complementary to one another and mutually reinforce and enhance each other the result is that the dosages can be kept extraordinarily small. A tablet contains 0,6 grams of Bromide and 0,04 grams of Natrium-phenylethyl-barbituricum. For this reason, Lubrikal, therefore, can be taken in the customary therapeutic dosages without approaching the tolerance limit and is equally suitable for treatment of adults and children.

How the Lubrokal Cure Achieves its Results

Lubrokal is perfectly adapted for the cure of insomnia. The bromide component, systematically used, soothes the cortical nerve centers and stops the flow of disturbing impulses to the centres of sleep, which, on the other hand, are so soothed and relieved that they are again able to assume their normal function. Any other source of disturbance is removed by a dosage of Barbituricum so slight, that in other circumstances it would have hardly any effect at all

Naturally, states of irritation of the nervous system which are of long standing, especially those which are constitutional, will not disappear spontaneously through the mere use of a few of the tablets. If Lubrokal is to have a fair chance to exert its curative influence, and if it is desired that a lasting cure be achieved, then a sustained and gradual treatment of the nerve centres in question must be undertaken. A state of repose is induced by the medium which necessarily brings in its train a gradual soothing of the frayed nerves which will continue after the treatment has been completed and the dosages can then be broken off.

A dosage of Lubrokal can be compared to a bandage on a wound. The bandage, of course, does not heal the wound, but it keeps it undisturbed from exterior influences and enables the process of healing to go on, and nature does the rest.

Carrying Out of the Cure

A necessary pre-condition of restored health is a sound hygiene of sleep. The patient should keep regular

hours for repose and if otherwise in good health he should not sleep longer than from eight to nine hours each night, although he may lie down for half an hour before retiring. Sound sleep is in some cases achieved in the first night or two, but more often after the third or fourth night. This happens because in the first night or so the smallness of the bromide dosage is not sufficient to soothe the nerve centres completely and so the sleep centres still receive disturbing impulses from the relevant source which cannot be overcome by the slight barbituric dosage taken. It is only after the bromide has had time to do its work on the nerves that the barbituric can fully operate to induce sleep. It is for this reason that the patient should be told not to expect sound sleep in the first few nights.

If, after the treatment has been carried on for about a week there appears to be no improvement then the dosage should be increased by half a tablet. Higher dosages than three tablets are very seldom called for; more often sound sleep supervenes in the first few nights so that after a week's treatment the dosage can be reduced by half a tablet. It should be said that the very smallest dosage which will induce sound and regular sleep is the correct one. Treatment, according to the severity of the ailment, should be proceeded with for from a matter of a few weeks to several months. In by far the most cases sleep is deep and regular during the course of the cure. The patient, with the right dosage, feels fresh and well and not only enjoys sound sleep at night, but is less fretful and more at ease in the daytime. This tranquillizing effect of the Lubrokal cure is much more pleasant for the patient compared with treatment with pure barbituric derivatives.

It sometimes happens that without any apparent cause at all sleep becomes suddenly disturbed and fitful in the middle of the cure. This is by no means a sign that Lubrokal has lost its influence or that the patient has become accustomed to the dosage and has become immune to its effects. If this happens, the dosage must be increased at once by one whole tablet for a period of a week, after which the patient goes back to the dosage which was formerly sufficient. Such disturbances, however, are comparatively rare. Then there are sources of excitement outside which are sometimes greater than the patient is able to bear, and sleeplessness ensues once more as a result. Even in such cases, however, it will suffice if the dosage is increased by one tablet for from eight to fourteen days, and after the disturbance has been overcome the patient can go back to the former dosage.

A greater difficulty than the carrying through of the cure is that represented by knowing when to bring it to an end. In the first place, it is not always easy to recognize whenthe patient has so far progressed that the dosage can begin to be lessened. Chronic cases generally require a course of treatment lasting several months. But even when the patient appears to be well, is sleeping soundly at night, and is his former bright self in the daytime the dosage should never be broken off abruptly; he must gradually be weaned away from them. There is no formula which can be prescribed as sure; the best method is to proceed as follows:- the dosage is reduced by half a tablet and this is continued for from fourteen days to three weeks. If the patient continues to sleep well, then the dosage should be reduced again by one half or one quarter of a tablet. After a like period, if no harm results, it should be decreased once more by the same amount, and in this way the patient is restored to healthful and natural sleep until the time comes when treatment can be terminated.

In especially difficult and chronic cases, even Lubrokal will not achieve a complete cure; in truth- no real cure for such states is brought about, and the patient feels much better after a Lubrokal course than before. Treatment can be suspended for a few months and then restarted. In this way, it is often possible to see a great improvement in the state of the sufferer. Cases are known in which, after the Lubrokal cure has been repeated several times, even severe constitutional cases have been greatly assisted.

A doctor will now ask whether it is possible to administer a medicine which contains bromide and barbituric over a period of months without injuring the general health of the patient. We would point to the smallness of the amount of such components in the tablets. Since, even with the maximum dosage in the middle of the cure of chronic cases only from one and a half to two and in some cases- only one tablet is taken each night there need be no fear of harmful results for the patient. In cases of epilepsy, for instance, much higher dosages of Lubrokal can be given over a period of years, without any dleterious effect being observed. There is, therefore, nothing which need stop a conscientious doctor from using Lubrokal to cure sleeplessness.

Bromide acne, which sometimes occurs, can be banished through the addition of from three to four drops of liquid calli arsenicosi to the Lubrokal solution. Slight headaches, which are sometimes felt after awakening in the morning, generally disappear after an hour or two but can

be got rid of more quickly by giving the patient a cup of strong coffee or 0,1 g of Caffein in warm water. A slight feeling of tiredness during the day which sometimes occurs will disappear of its own accord after treatment has been going on for a little time. If it does not, however, it should be taken as a sign that the dosage is too hight.

Important Precautions

Lubrokal tablets must be taken in at least a half or one whole wineglassful of cold or lukewarm water (not hot water!). It is very foolish to imagine that possible stomach-ache can be avoided by taking the tablets in a very small quantity of water or by swallowing them first and then drinking some. Children and patients with a sense of taste which is unusually sensitive should have the tablets given to them in a sweet drink or in slightly salted beef-tea.

Advantages of the Lubrokal Cure

The greatest advantage of the Lubrokal form of treatment is that is a form of causal therapy for the relief of insomnia. It banishes the primary causes which have their origin in the nervous system. By a secondary effect exerted on the centres of sleep in the brain it then induces a habit of sound dreamless sleep. And-since in most cases of sleeplessness there is a history of nervous disorder it can be looked on as a form of therapy in which both forms of treatment are united. Results are achieved which could only be expected in other cases with the use of several different mediums or other complicated forms of treatment. The correct dosage,- easily established,- will banish the tendency to nervous irritation, improve the powers of concentration, and causes slight feelings, as for instance, of fear, anxiety, or depression to disappear. For this reason, most patients learn to take the medicine in spite of its bitter flavor, when they learn how much good it does them.

Compared with purely barbituric sleeping drafts the quantity of barbituric acid in Lubrokal is slight. Each tablet contains only 0,04 g Natrium-phenylethyl-barbituricum. Lubrokal, therefore, if taken as prescribed, is very easily tolerated and specially adapted for short cures.

Very important is the fact that taking the tablets never grows to be a habit which cannot be broken off; experience in treatment of epilepsy cases has fully confirmed this. Even after a patient has been receiving the treatment for a period of months the habit can be broken off from one day to the next. It is true that if the cure has not been completed, breaking off treatment will only mean that sleeplessness will supervene once more, but this can

hardly be considered as the fault of the medicine.

Finally, Lubrokal is a useful adjunct to other forms of treatment for nervousness and sleeplessness. Since it soothes the nerves of the patient and accustoms him to the enjoyment of proper repose it is a preliminary of many other forms of medical and psychotherapeutic cures.

APPENDIX 2

XYLIDRIN

Reduces inflammation - deadens pain - kills bacteria

Treatment of inflammatory process of the mucous membranes has no doubt been rendered easier by the adoption of mediums which reduce swelling. But complete treatment of the trouble must include something more than the mere soothing of an ailing organ. It is for this reason that we have been at pain to develop new bodies out of the amino-alcohol series, which not only bring about a decrease in inflammation of the mucous membranes, but which also exert strong anaesthetic and bacteria-destroying effects. The combination of two homologues of this series has been made up by us in various special forms and placed on the market under the name of Xylidrin.

Compared with Adrenalin and Ephedrin, Xylidrin displays a much greater range of effect and over and above this, it causes no increase in blood-pressure which would have any effect so far as medical treatment is concerned. Further, its anaesthetic properties are such that it can be said to rank with the best-known local anaesthetics so far perfected. But even from the bacteriological viewpoint we were able to increase greatly its range of effect. In truth, it appears that it is due to its germ-destroying powers that the basis is formed for the decrease of inflammation.

QUALITIES

Reduces inflammation - deadens pain - kills bacteria

For testing the germ-destroying properties of this preparation Phenol was chosen as a basis of comparison. Experiments showed that, the time taken by both substances being the same, notably weaker concentrations of Xylidrin were required for destruction of the germs present.

A test of its anaesthetic properties was made with the usual brush methods on the eyes of rabbits. A comparison with other surface anaesthetics showed that in duration of anaesthetization Xylidrin was noticeably superior to these, when a pressure of 8 g. was taken as complete anaesthetization. Its effect in decreasing inflammation of the mucous membrane was shown by clinical tests to be unusually lasting. Undesired concomitant phenomena were not observed. For Rhinitis Acuta and chronica, Rhinitis

Vasomotorica, Sinusitis, Hay Fever, a quick working solution and a mild nasal salve are on sale.

Liquid Xylidrin - Flask with drop syringe.

Xylidrin Nasal Salve - in tubes.

For the treatment of Haemmorrhoids, Anal ailments, Proctitis, there areXylidrin preparations on sale in tubes and in ointment form.

These are Xylidrin Haemorrhoid Salve.

Xylidrin Haemorrhoid Lotion.

The Albert Chemical Works - Wiesbaden-Biebrich.